Docket No.: PC9344BRTR (121*254)
(PATENT)



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Hua Z. Ke et al.

Application No.: 09/736051 Art Unit: 1654

Filed: December 13, 2000 Examiner: L.N. Leary

For: COMBINATION THERAPY FOR OSTEOPOROSIS

## RESPONSE TO NON-FINAL OFFICE ACTION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

### Introductory Comments

In response to the Office Action dated October 8, 2003 (Paper No. 21), Applicants respectfully request reconsideration of the rejections in view of the following comments.

Applicants acknowledge with appreciation the withdrawal of the finality of the Office Action dated February 4, 2003 and the removal of the rejections presented in that Office Action. Applicants also appreciate the allowance of claims 1-4, 6-14, 16-30, 33-42, 45-50, 52-55, 57-62, 65-69, 72-75, 79, 80, 84-89 and 92, and that claims 94, 96, 98, 100, 103, 105, 107 and 108 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 93, 95, 97, 99, 101, 102, 104 and 106 stand rejected under 35 USC 102 (b) and/or 103(a).

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**The 35 U.S.C. §§102(b)/103(a) Rejection of Claims 93, 97, 101-102 and 106**

Claims 93, 97, 101-102 and 106 stand rejected as allegedly being anticipated by or, in the alternative, being obvious over Lax et al. (Endocrinology, 1983, 113(5), 1043-1045). Applicants are providing a new copy of the Lax et al. reference, for submission in a supplemental information disclosure statement, because portions of the reference provided by the Patent Office were missing.

The Patent Office asserts that Lax et al. disclose the administration of combinations comprising growth hormone and tamoxifen to rats, and that this disclosure renders claims 93, 97, 101-102 and 106 either anticipated or obvious.

Three of the rejected claims are independent. Independent claim 93 is directed to a combination comprising an estrogen agonist/antagonist and a growth hormone secretagogue. Independent claim 102 is directed to a pharmaceutical composition comprising an estrogen agonist/antagonist, a growth hormone secretagogue and a pharmaceutical carrier. Independent claim 106 is directed to a process for making a pharmaceutical composition by combining an estrogen agonist/antagonist, a growth hormone secretagogue and a pharmaceutical carrier.

Each of the rejected claims requires a combination of an estrogen agonist/antagonist and a growth hormone secretagogue. Yet nowhere does the Lax et al. reference disclose administration of such a combination. The Office Action refers to page 1045 as disclosing administration of human growth hormone and tamoxifene. Yet at this page, Lax et al. disclose that rats implanted with minipumps that administer growth hormone are administered either DHT (an androgen) or DES (an estrogen) alone or in combination with monohydroxy tamoxifen (MHT). *See* Lax et al., page 1045, column 1, lines 8-10. Thus, the Patent Office has not shown that Lax et al. discloses any composition comprising both growth hormone and an estrogen agonist/antagonist. Lax et al. only discloses separate administration, via minipump, of the growth hormone and via injection of DHT, DES or MHT.

Furthermore, as the Examiner acknowledges, Lax et al. does not disclose growth hormone secretagogues. The Office Action states that human growth hormone has an inherent

secretagogue function. Office Action, page 3. Applicants respectfully disagree. The term growth hormone secretagogue refers to compounds that stimulate the release of growth hormone or mimic the action of growth hormone as described at page 32, lines 27-29 of the specification. Growth hormone itself is a large polypeptide molecule of varying amino acid sequence depending on species of origin. Human growth hormone, for example, is a single polypeptide chain of 191 amino acids having a molecular weight of over 22,000. *See* page 1488 of the Merck Index, Twelfth Edition, copy filed herewith with Information Disclosure Statement.

Contrary to the Examiner's assertion, growth hormone itself does not stimulate the release of growth hormone and thus is not a "secretagogue." The Lax et al. reference lacks any suggestion or motivation to employ a growth hormone secretagogue in place of growth hormone. For these reasons the Lax et al. reference does not anticipate or render obvious independent claims 93, 102 and 106, or the related dependent claims.

Dependent claims 97 and 101 are directed to a method of treating a condition that presents with low bone mass, such as osteoporosis, using a composition comprising a combination of a growth hormone secretagogue and an estrogen agonist/antagonist. The Lax et al. reference does not disclose any method whatsoever of treating a condition that presents with low bone mass. Instead, Lax et al. discusses the effects of estrogens and growth hormone on three hepatic enzymes. For this additional reason, Lax et al. neither anticipates nor renders obvious the methods of claims 97 and 101.

**The 35 U.S.C. §103(a) Rejection of Claims 93, 95, 97, 99, 101-102, 104 and 106**

Claims 93, 95, 97, 99, 101-102, 104 and 106 stand rejected as allegedly being obvious over Gertz et al. (WO 95/11029, April 1995) in view of Wronski et al. (Endocrinology, 1993, 132(2), 823-831) and Evans et al. (Endocrinology, 1994, 134(5), 2283-2288, Abstract Only). Applicants are providing a new copy of the Wronski et al. reference, for submission in a supplemental information disclosure statement, because portions of the reference, as provided by the Patent Office, were missing. Applicants are also providing the full Evans et al. article, because the Patent Office provided only a copy of the abstract.

Gertz et al. is directed to combinations of a bisphosphonate and a growth hormone secretagogue and treating osteoporosis with those combinations. As the Examiner admits, Gertz et al. does not disclose a combination of an estrogen agonist/antagonist and a growth hormone secretagogue. Wronski et al. discloses monotherapy with parathyroid hormone (PTH), estrogen or a particular bisphosphonate, risedronate, and combination therapy of PTH and estrogen or PTH and risedronate. Wronski et al. does not disclose or suggest any combinations comprising an estrogen agonist/antagonist.

The Examiner stated that Wronski et al. provided sufficient guidance to allow a skilled artisan to use estrogens and bisphosphonates interchangeably for treating bone mass loss, and therefore it would have been obvious to substitute estrogens for the bisphosphonates in Gertz et al. to obtain the combinations of Applicants' invention.

Applicants respectfully disagree. An estrogen agonist/antagonist is not equivalent to an estrogen. The compounds of the compositions and methods of the present claims are not natural or synthetic estrogens, but are estrogen agonists/ antagonists, which are also known as selective estrogen receptor modulators (SERMs). SERMs, unlike estrogens, can act as an estrogen receptor agonist in some tissues and as an estrogen receptor antagonist in other tissues. The specification identifies many known SERMs at page 16 to page 29. Because an estrogen agonist/antagonist is not equivalent to estrogen, even if a skilled artisan made the substitution suggested by the Examiner of taking the bisphosphonate/growth hormone secretagogue combination of Gertz et al. and substituting the estrogen disclosed in Wronski et al. for bisphosphonate, the artisan would still not obtain Applicants' claimed invention.

Furthermore, there is no suggestion to replace the bisphosphonate in the combination of Gertz et al. with estrogen. The Examiner refers to a statement in Wronski et al. attesting to similar activity for estrogen and bisphosphonates: "Estrogen (1,2) and bisphosphonates (3-5) have been shown to depress bone resorption and increase bone density modestly in women with established osteoporosis, but their ability to completely restore the lost bone is uncertain." Yet a statement of similar activity and similar unknown effects does not rise to the level of a suggestion to substitute the two compounds with a reasonable expectation of success in

combination with a growth hormone secretagogue. The Examiner also refers to Wronski et al. as showing results of a comparative study of estrogens and bisphosphonates for treating lost bone mass. Yet comparing the effects of two medicinal compounds is not a suggestion that the two are interchangeable, let alone interchangeable in combination with another drug, which is not discussed in the Wronski et al. reference, with an expectation of success.

Furthermore, Wronski et al. teaches that use of estrogen or a bisphosphonate in certain combinations is not significantly advantageous over monotherapy for treating bone loss. Wronski et al., pages 828-231. Wronski et al. teaches that combination therapy with PTH and estrogen in OVX rats is less effective than treatment with PTH alone. The author characterized this result as disappointing. Wronski et al. concluded that estrogen and bisphosphonate partially suppressed the stimulatory effect of PTH on bone formation. *Id.* at 829. With respect to the Wronski et al. reference, one of ordinary skill in the art could reasonably conclude that combination therapy with an estrogen or bisphosphonate is less desirable than monotherapy. Therefore, this reference does not suggest use of other combination therapy for treating bone loss. The failure reported with combination therapy reported in Wronski et al. does not suggest success in other combinations.

The Examiner relied upon Evans et al. as disclosing raloxifene as an estrogen agonist/antagonist. Evans et al. pertains to the effects of raloxifene as a monotherapy on tibia histomorphometry and does not disclose any combinations comprising raloxifene and another active agent. Accordingly, it does not provide the combinations or the suggestion to combine that is missing from the Gertz et al. and Wronski et al. references.

In sum, Applicants respectfully submit that one skilled in the art, at the time of the present invention and in possession of the Gertz, Wronski and Evans references, would not have found the present invention to be obvious over the combination of those references. First, Gertz et al. does not disclose or suggest a combination of a SERM compound and a growth hormone secretagogue or that such a combination can be used for the treatment of a condition that presents with low bone mass. Second, Wronski et al. does not provide the suggestion to substitute a SERM compound in the method of Gertz et al. because Wronski et al. discloses estrogen, but not

SERM compounds. Wronski et al. also teaches away from combination therapy with estrogen or bisphosphonate, as it reports experiments that showed no significant advantage in combination with PTH over monotherapy with PTH. Third, Evans et al. does not disclose or suggest any combinations comprising the estrogen agonist/antagonist raloxifene. Thus, the combination of Gertz et al., Wronski et al. and Evans et al. in no way discloses, teaches or suggests to one skilled in the art a combination of an estrogen agonist/antagonist and a growth hormone secretagogue or a method of treating a condition presenting with low bone mass with such a combination.

For these reasons, applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103(a) of claims 93, 95, 97, 99, 101-102, 104 and 106.

**Conclusion**

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue.

Enclosed is a petition for a three-month extension of time and a supplemental Information Disclosure Statement with authorization to charge the requisite fees. No additional fees are believed due. However, if any fees are due and unpaid concerning the filing of this paper, please charge our Deposit Account No. 03-2775, from which the undersigned is authorized to draw.

Dated: April 8, 2004

Respectfully submitted,

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